

Oxygen Ethers of the Type
—N:C.(OR), Derived from Certain
Nitrogen Heterocycles

DISSERTATION

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIRE-
MENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY,
IN THE FACULTY OF PURE SCIENCE OF COLUMBIA
UNIVERSITY

BY

CLARENCE EARL MAY, B.A., M.A.,

NEW YORK CITY

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EASTON, PA. :
ESCHENBACH PRINTING COMPANY.
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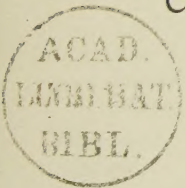
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Acknowledgment.

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ACKNOWLEDGMENT.

This work was carried out under the supervision of Professor Marston Taylor Bogert. Whatever merit this research may possess, the credit is all due Professor Bogert, for by his personal efforts, the work was made possible. It is with great pleasure that I have the opportunity to thank him for the many kindnesses and suggestions throughout the work.

CLARENCE EARL MAY.
May, 1908.

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INTRODUCTION.

It has been known for a long time that where we have a carbonyl group adjacent to an imino group, or in other words, an amide structure— CO.NH —tautomerism arises and we have compounds deporting themselves as of different types. Such compounds may exist in the form already mentioned, or one may have the tautomeric form, —COH=N— , the true "enolic" structure, or we may have a mixture of the two forms in equilibrium. Considerable work, extensive rather than intensive, has been done in the α -pyridone, α -quinolone and α -pyrimidone series, where we have the same conditions for tautomerism. In these series, the tautomerism has been the subject of much discussion with regard to the exact structural formula, whether "enolic" or "ketonic," by which the pyridine and quinoline derivatives could be best represented.

In a recently published article, Bogert and Seil,³⁶ have given an important resumé of this type of tautomerism in the pyridine, quinoline, pyrimidine and quinazoline series, and have indicated the most important work that has been reported on the subject. The problem of finding in just what form the given α -pyridone, etc., exists, is a very delicate proposition. The true tautomers in the unsubstituted compound are as yet unknown, that is, they have never been separated in any single instance and proven to be either one or the other form. The only fact known is that under some conditions, the substance behaves as though it were a phenol, and then again as though it were a ketone. However, the same compound shows the two different deportments, and in each case by a substance having a definite melting-point and non-separable even into closely melting tautomers.

From a study of the two groupings, —COH=N— and —CO.NH— , it is evident that by substitution of an alkyl radical for the hydrogen of the hydroxyl or the imino grouping, we would have isomers differing only in the fact that there is a nitrogen linkage in one case, and in the other, the union of the alkyl radical to the molecule is by means of an oxygen atom. To obtain the respective compounds where the hydrogen atoms were each replaced by the same alkyl radicals, has been an interesting subject with previous workers. In fact, there has been no very rigid method of operation to be carried out, whereby the operator could depend on getting the exact tautomeric derivative he desired.

Three methods for forming these tautomeric forms of the alkyl derivatives of α -pyridone, α -quinolone and, to a lesser extent, of α -pyrimidone, have been tried. By the action of alkyl halide on the silver salt of the desired compound, one should obtain a compound with oxygen linkage between the alkyl group and the rest of the molecule. By the action of the alkyl halide on the alkali salt of the α -hydroxy pyridine, etc., one should get an alkyl nitrogen or alkyl oxygen linkage. If the alkali reacts with the compound existing in the "enolic" form, to give a phenolate, then by subsequent treatment with the alkyl halide, the alkyl group would have an oxygen linkage. If, however, the alkali reacts with the imino group, a nitrogen attachment would result from the interaction of alkyl halide. By the action of alkali alcoholate, on the halogen derivative of the α -pyridone, etc. (since the compound seems to exist in the "enolic" form whereby the hydroxyl group is replaced by halogen on treating with PCl_5), one should obtain a compound with an oxygen linkage between the alkyl group and the rest of the molecule. If the compound before halogenation (usually chlorination) does not already exist in the "enolic" form, it is observed that two halogens might replace the oxygen atom of the carbonyl group, and

at the same time lose HCl, a hydrogen atom coming from the imino group, thus giving the same chloride as though the original substance had reacted in the "enolic" form.

In the practical applications of these methods outlined, as a rule, they hold fairly well; however, there are cases of their application where the results are in distinct disagreement with any general conclusions that might be drawn with regard to the methods themselves. Hantzsch,⁵ by the action of methyl iodide on the sodium salt of α -hydroxy lutidine, formed the nitrogen methyl ether only. The same type of reaction was reported by Von Pechmann and Welsh,⁴ where they obtained the nitrogen ether by allowing methyl iodide to react with di-sodio derivative of α -hydroxy nicotinic acid. Friedländer and Ostermaier,¹ by the action of ethyl iodide on the sodium derivative of carbostyryl, work which was confirmed in this laboratory, obtained nitrogen and oxygen ethers at the same time. Oxygen and nitrogen ethers were obtained by Knorr,¹¹ by the action of methyl iodide on the sodium salt of α -hydroxy- γ -methyl-quinoline (α -hydroxy lepidine).

By allowing methyl iodide to react with the silver salt of α -hydroxy pyridine, Von Pechmann and Baltzner,¹⁶ formed about equal parts of oxygen and nitrogen ethers. By allowing ethyl iodide to react with the silver derivative of carbostyryl, Friedländer and Weinberg³ prepared the ethyl oxygen ether of carbostyryl in quantitative yield. Wenzel,²⁰ by the action of alkyl halides on the silver salt of γ -hydroxy quinoline (kynurine), obtained nitrogen ethers. By the action of alcoholic KOH on α -chlorquinoline, Friedländer and Ostermaier² prepared the oxygen ether of the quinoline. Wenzel²⁰ prepared the nitrogen ether by allowing sodium alcoholate to react with α -chlorquinoline.

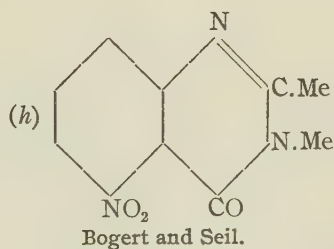
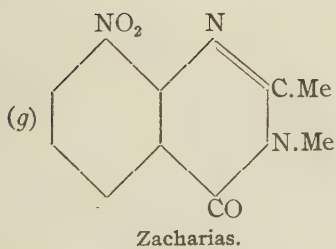
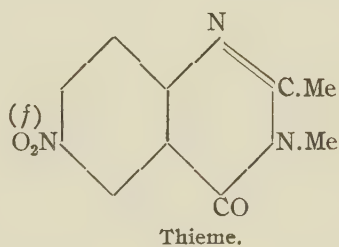
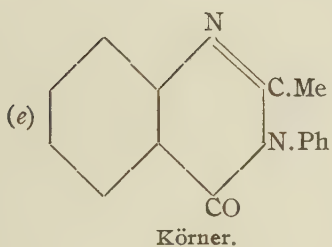
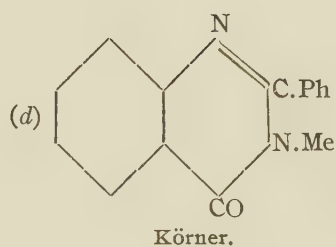
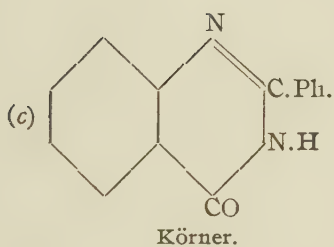
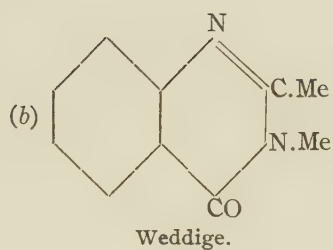
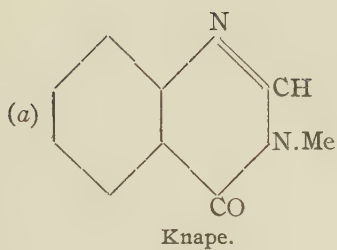
Ether Formations in the Pyrimidine Series.

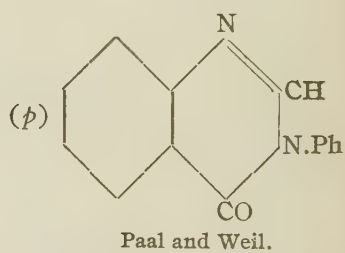
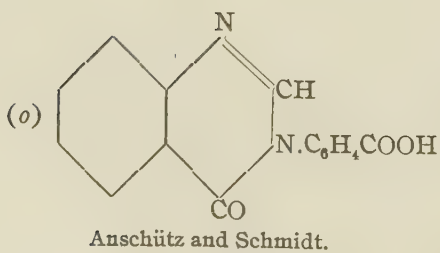
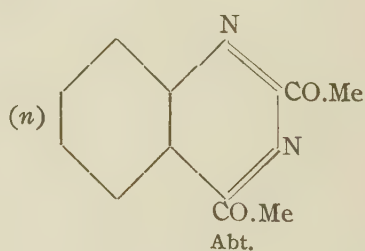
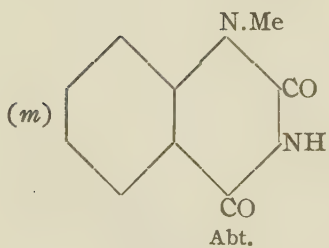
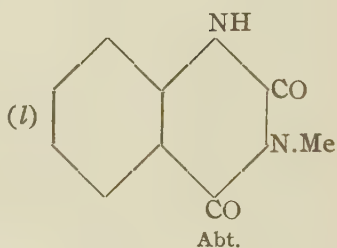
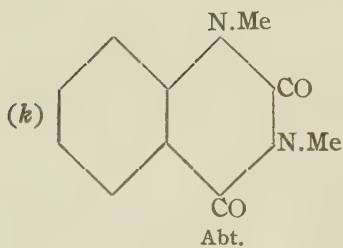
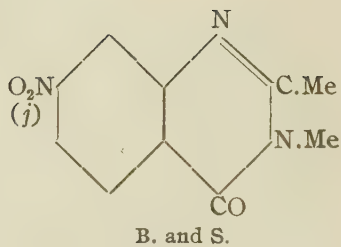
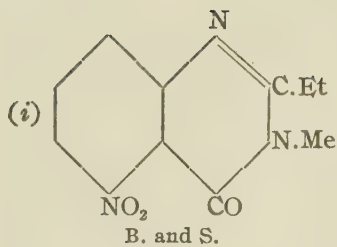
Büttner,³² by the chlorination of barbituric acid, obtained 2,4,6-trichlorpyrimidine, which he converted into

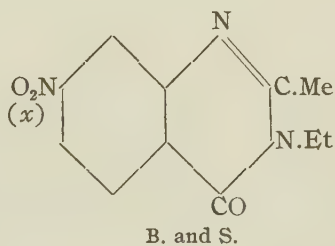
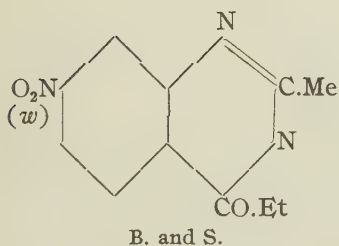
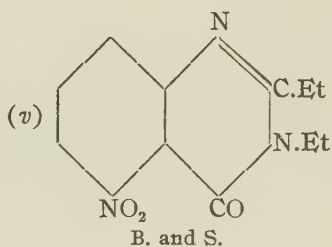
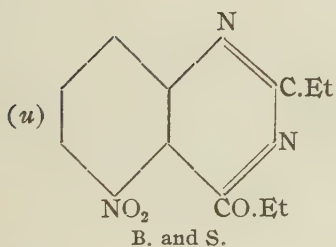
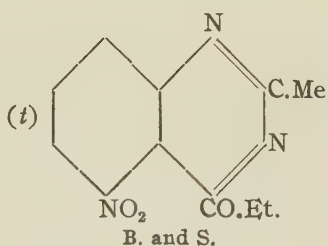
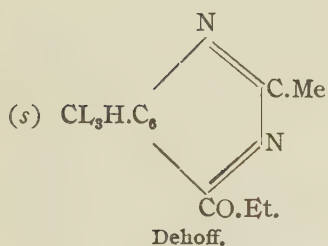
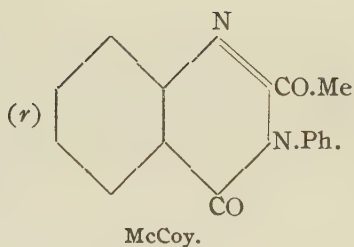
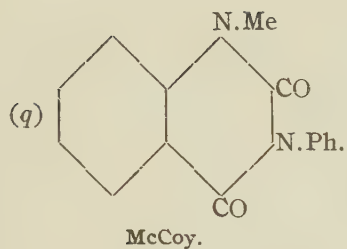
2,4,6-trimethoxy pyrimidine by the action of sodium methylate. By using less alcoholate, he also prepared 2,4,6 (or 4,6,2) dimethoxy chlorpyrimidine.

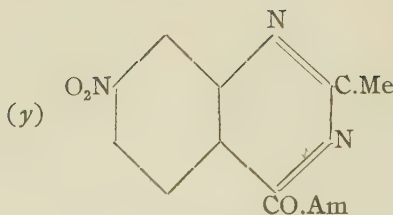
Angerstein²⁸ prepared 4,6-dimethyl 2-methoxy pyrimidine and also the corresponding 2-ethoxy and 2-phenoxy pyrimidine, by allowing the respective alcoholates to react with 2-chlor, 4,6-dimethyl pyrimidine. Schlenker²⁷ prepared 4,5-dimethyl 2,6-dimethoxy pyrimidine by allowing sodium methylate to react on the 4,5-dimethyl 2,6-dichlorpyrimidine. Gabriel and Colman²⁶ made 4-methyl 2,6-dimethoxy pyrimidine by the interaction of sodium methylate and 4-methyl 2,6-dichlorpyrimidine. The same authors,³³ by the reduction of 2,6,4-dimethoxy chlorpyrimidine, made by Büttner by the partial alkylation of 2,4,6-trichlorpyrimidine, obtained 2,6-dimethoxy pyrimidine. The monomethoxy pyrimidine was formed in the same way by reducing methoxy dichlorpyrimidine.

Johnson and Heyl,³⁷ by the interaction of methyl iodide and the silver salt of 2-anilino 6-hydroxy pyrimidine, formed 2-anilino 6-methoxy pyrimidine. By allowing methyl iodide to react with the sodium derivative of 2-anilino 6-pyrimidone, they obtained both the oxygen and nitrogen tautomers, the 1-methyl 2-anilino 6-pyrimidone and the 2-anilino 6-methoxy pyrimidine. These compounds were formed at the same time. By the interaction of sodium ethylate and 2-ethylmercapto 5-ethoxy 6-chlorpyrimidine, there was formed 2-ethylmercapto 5,6-diethoxy pyrimidine. Stokes and Von Pechmann,⁸ by the action of NaOH and ethyl iodide on 1,2,4-trichlor 3-amino 5-hydroxypyridine, formed the corresponding 1,2,4-trichlor 3-amino 6-ethyl pyridine. Also by the action of sodium methylate on 1,2,4,5-tetrachlor 3-aminopyridine, they formed 1,2,4-trichlor 3-amino 5-methoxypyridine; sodium ethylate gave the corresponding ethyl oxygen ether.









B. and S.

Ether Formation in the Quinazoline Series.

By allowing methyl iodide to react with the sodium salt of 4-quinazolone, forming the corresponding 3-methyl 4-quinazolone,^(a) Knape¹⁵ obtained a very clean reaction with the formation of the nitrogen ether. Weddige,⁹ by the interaction of acetic anhydride and *o*-aminobenzmethylamide, and also by the methylation of 2-methyl 4-quinazolone sodium salt, with methyl iodide, formed 2,3-dimethyl 4-quinazolone.^(b) Körner,¹⁰ by allowing benzoyl chloride to react with *o*-aminobenzamide, following with the anhydride formation, obtained 2-phenyl 4-quinazolone.^(c) By the action of benzoyl chloride on *o*-aminobenzmethylamide, followed by dehydration, obtained 2-phenyl 3-methyl 4-quinazolone.^(d) The same compound was also obtained by the action of methyl iodide on the sodium salt of 2-phenyl 4-quinazolone. By the dehydration of *o*-acetaminobenzanilide, he also formed the 2-methyl 3-phenyl 4-quinazolone.^(e)

Thieme,¹⁸ obtained a quantitative yield of 2,3-dimethyl 6-nitro 4-quinazolone^(f) from the action of methylamine and ethyl *m*-nitro *o*-acetaminobenzoate.

Zacharias¹⁷ prepared 2,3-dimethyl 8-nitro 4-quinazolone^(g) very easily by the action of methyl iodide on the sodium salt of 2-methyl 8-nitro 4-quinazolone.

Bogert and Seil,³⁶ by the action of methyl iodide on the potassium salt of 5-nitro 2-methyl 4-quinazolone, formed the 5-nitro 2,3-dimethyl 4-quinazolone,^(h) and with the potassium salt of 5-nitro 2-ethyl 4-quinazolone and methyl iodide,

formed the 5-nitro 2-ethyl 3-methyl 4-quinazoline.⁽ⁱ⁾ They also formed the 7-nitro 2,3-dimethyl 4-quinazoline,^(j) by the methylation of 7-nitro 2-methyl 4-quinazoline, and by the action of 4-nitro acetanthranilic acid with methylamine.

Abt,¹² by the action of methyl iodide on the disodium salt of benzoylene urea, formed the 1,3-dimethyl benzoylene urea.^(k) The mono-methyl (3) benzoylene urea was^(l) formed by the condensation of *o*-aminobenzmethylamide and urea. Mono-methyl (1) benzoylene urea^(m) was prepared by the action of *o*-methylamino benzamide and urea. The 2,4-dimethoxy benzoylene urea⁽ⁿ⁾ was prepared from 2,4-dichlorquinazoline and sodium methylate.

Anschütz and Schmidt,³⁰ independently of the ordinary ether-formation methods, prepared *o*-carboxylic-phenyl (3), 4-quinazoline^(o) by heating formyl anthranilic acid.

Paal and Weil,¹⁹ in an entirely independent method, prepared the 3-phenyl nitrogen ether of benzoylene urea.^(p)

McCoy²⁵ prepared 1-methyl 3-phenyl benzoylene urea^(q) by allowing methyl iodide to react with the potassium salt of 3-phenyl benzoylene urea. The tautomeric oxygen ether, 2-methoxy 3-phenyl 4-quinazoline^(r) was made by the same author by allowing sodium methylate to react with 2-chlor 3-phenyl 4-quinazoline.

Dehoff,¹⁴ by the action of ethyl alcoholic KOH on Bz. trichlor 2-methyl 4-chlorquinazoline, formed the corresponding Bz. trichlor 2-methyl 4-ethoxyquinazoline.^(s)

Bogert and Seil,³⁶ by the action of ethyl iodide on the alkali salt of 2-methyl 5-nitro 4-quinazoline, formed 2-methyl 5-nitro 4-ethoxyquinazoline.^(t) By a similar ethylation of 5-nitro 2-ethyl 4-quinazoline, the same authors prepared 2-ethyl 5-nitro 4-ethoxyquinazoline,^(u) which, by alcoholic crystallization, changed over to the tautomeric nitrogen ether.^(v) While working with 7-nitro 2-methyl 4-quinazoline, by means of ethyl iodide and the alkali salt, they prepared 7-nitro 2-methyl 4-ethoxyquinazoline.^(w)

The corresponding nitrogen ether^(x) was identical with the condensation product resulting from the action of methylamine and 4-nitro acetantranil. The same authors prepared 7-nitro 2-methyl 4-isoamyloxyquinazoline^(y) by the interaction of isoamyl iodide and the sodium salt of 7-nitro 2-methyl 4-quinazolone.

Alkylations in the Quinoline Series.

The first work done in this research on the alkylation of nitrogen heterocycles, was a repetition of the work of Friedländer and Ostermaier,¹² and Friedländer and Weinberg.³⁶ Carbostyryl was made from *o*-aminocinnamic acid and converted to the chloride; the latter was treated with sodium ethylate and converted into α -ethoxy quinoline. No nitrogen ether was observed. The oxygen ether, volatile with steam, yielded a mercury salt with mercuric chloride, melting at 136–8° C. By the action of ethyl bromide on the sodium salt of carbostyryl, the latter prepared by dissolving the carbostyryl in absolute ethyl alcohol containing the calculated amount of sodium, there resulted about equal parts of ethyl oxygen and nitrogen ethers. The same result was obtained by the action of ethyl iodide on the sodium salt of carbostyryl. α -Chlorquinoline and sodium isoamylate gave oxygen and nitrogen ethers in the proportion of 5 : 1 respectively. With HgCl_2 , the oxygen ether formed a less soluble mercury salt melting at 120–130° C. The oxygen ether with HCl , hydrolyzed to form carbostyryl, melting at 196° C. The mercury salt of the nitrogen isoamyl ether melted at 89–90° C., and was obtained as long needles quite soluble in dilute HCl . By the action of isoamyl iodide on the sodium salt of carbostyryl, both oxygen and nitrogen ethers were formed. With isoamyl iodide and silver carbostyryl, a small amount of nitrogen ether resulted.

α -Hydroxy lepidine, prepared from acetoacetanilid by Knorr,¹¹ was converted to the sodium derivative by sodium ethylate and allowed to react with isoamyl iodide. There

resulted a colorless product distilling above 360°C ., melting at $120\text{--}40^{\circ}\text{C}$., hydrolyzing by boiling a few minutes with HCl to form a product melting at $213\text{--}5^{\circ}\text{C}$., which was identical with α -hydroxy lepidine. Evidently the product of alkylation was an oxygen ether.

Discussion.

In the course of this work, a few compounds already known in the literature, and several new compounds filling in the gaps, have been made in this laboratory. The main point of the work has been the study of the methods of preparation and the properties of the nitrogen and oxygen ethers in the quinazoline series. This work included the methyl, ethyl, normal propyl and normal butyl ethers (both oxygen and nitrogen respectively) of 4-quinazolone, the methyl and ethyl oxygen ethers of Bz. trichlor 2-methyl 4-quinazolone, and the methyl, ethyl and normal propyl ethers (both oxygen and nitrogen) of benzoylene urea.

In the study of these compounds, the ethers were made by two general methods: first, by making the sodium salt of the quinazolone and allowing the desired alkyl halide to react, with the elimination of sodium iodide; second, by chlorinating the quinazolone (replacing the phenolic hydroxyl by chlorine) and allowing the desired alcoholate to react. From the experience of previous workers, oxygen ethers were always looked for in the preparation of nitrogen ethers by the first method. By steam distillation, with which the oxygen ethers are easily volatile, the separation of these ethers, if present, was brought about. The residue from steam distillation contained the nitrogen ethers which were recovered by crystallization from water. By the first method of ether-formation, nitrogen ethers exclusively resulted. In this connection, it was found that some of the nitrogen ethers were not absolutely non-volatile with steam. The nitrogen ethers isolated were colorless, odorless solids quite soluble in water and possessing a melting point higher than the corre-

sponding oxygen tautomer. With strong HCl, the nitrogen ethers were not hydrolyzed.

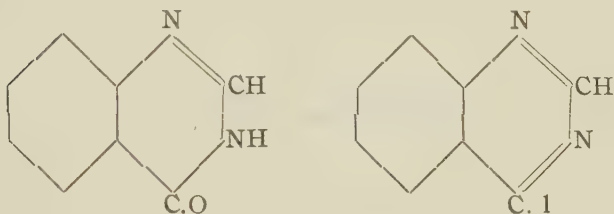
By the second method of ether formation, the reaction mixture was always steamed, to separate the oxygen ether from the unsubstituted quinazolone resulting from the hydrolysis of the chloride. By ether extraction of the water distillate, the oxygen ether was collected, dried and obtained in an analytically pure form as a rule, after the removal of the ethyl ether. In every case tried, the oxygen ethers were found to distil readily with steam, separating in the distillate as almost insoluble oils, which in the benzoylene urea series, solidified on refrigeration. On hydrolysis with strong HCl, the oxygen ethers were found to hydrolyze, yielding the hydroxy quinazoline. Oxygen ethers were found to melt lower than their tautomers, to have an ethereal odor, to be less soluble in water, but more soluble in HCl.

According to the literature, the nitrogen ether is regarded as the much more stable form of the two tautomers and various authors have succeeded in actually converting oxygen ethers into true nitrogen ethers by different methods of heating. Haitenger and Lieben,⁶ while working with γ -methoxy pyridine, formed by the action of NaOMe on γ -chlorpyridine, found that on distilling the oxygen ether at 220° C., a residue of nitrogen ether remained in the flask. Knorr,¹⁰ while working with α -methoxy lepidine found that by heating the oxygen ether in a sealed flask, above the boiling point, there was a smooth conversion to the nitrogen ether. Meyer,¹² found that by heating γ -methoxy quinaldine to 260-70° C., the oxygen ether was largely changed to the nitrogen ether. Meyer,³² also found that methoxykynurine heated to 300° C., rearranged to the tautomeric form, and at 360° C., the ethoxykynurine suffered the same rearrangement. Bogert and Seil³³ found that by crystallization of their 2-ethyl 4-ethoxy 5-nitroquinazoline, the body suffered conversion to 2,3-diethyl 5-nitro 4-quinazolone.

In this research, the oxygen ethers prepared were quite

stable compounds and in no case was a rearrangement to the tautomeric form observed.

4-Quinazolone and 4-chlorquinazoline.



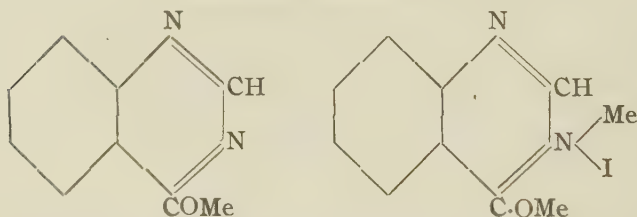
This simple quinazolone was easily prepared according to a method previously worked out by Niementowski.²² By fusing the anthranilic acid and formamide under an air condenser, at such a temperature that practically everything was condensed by the air condenser, and continuing the heating until the whole mass became solid, were found to be the best conditions for the preparation of this compound. By subsequent crystallization from boiling water, a very pure product, very much resembling paper pulp, was obtained. Melting point, 212°C .

The 4-chlorquinazoline was prepared by the directions of Gabriel,²³ whereby 4-quinazolone, resulting from the fusion mentioned above, was converted to the corresponding 4-chlorquinazoline. By repeated efforts, it was found that to get good results in the chlorination, the POCl_3 must be redistilled and double the quantity recommended by Gabriel gave a much cleaner product to work with. The PCl_5 from freshly opened bottles worked much better, and the purer the quinazolone, the less colored the end-product. Unless the conditions of chlorination and the purity of the reagents were closely watched, the final product would very likely be an intensely reddish colored mass. The best conditions found for the chlorination, were to use a large excess of POCl_3 , distilled previously, heat over a gauze and under an inverted cooler, usually an hour after complete solution takes

place; transfer the reaction mixture to a distilling flask, with the aid of fresh POCl_3 , distil off the excess of PCl_3 and POCl_3 using a free flame and normal air pressure. Toward the end of the distillation, a water bath was used for heating and vacuum distillation removed the last of the phosphorus halides.

With continued heating and reduced pressure, the chloride sublimed in fine needles almost filling the flask, but continued heating, even with the water bath, decomposed the residue in the flask, so purification by that method was abandoned. The chloride was simply melted down in a boiling water bath, poured out and weighed quantities used for the subsequent work.

4-Methoxyquinazoline.



In the preparation of this compound, 10 grams of 4-quinazalone were chlorinated, the reaction mixture freed of phosphorus halides and the total amount of chloride which had scarcely any color at all, was allowed to react with 75 cc. absolute methyl alcohol containing 2.5 grams metallic soda. A lively reaction, with the separation of NaCl , set in in the cold; the reaction mixture was heated under a water condenser for 3.5 hours on a water bath. The alcoholic solution was then filtered and evaporated to dryness and the residue subjected to steam distillation. The distillate came over milky, with a slightly yellow oil separating. On extraction with ether, drying with CaCl_2 and evaporation of the ether, the distillate yielded 4 grams of a thin oil, which on

standing at room temperature for a few minutes, crystallized in the form of warts and rosettes. These clumps of crystals became quite hard on standing in a desiccator and showed a melting point of 35.4°C . From the mother liquor of the steam distillation, 4 grams of the unchanged 4-quinazolone were obtained. Melting point 208°C .

By a Dumas N determination, 0.2 gram substance yielded 31.8 cc. N at 23°C . and 745 mm. pressure. Calculated, this gives 17.65 per cent N. The theory for nitrogen in $\text{C}_9\text{H}_8\text{N}_2\text{O}$ is 17.50 per cent.

By a carbon and hydrogen determination, 0.2 gram substance gave 0.0950 gram H_2O and 0.4938 gram CO_2 , which calculated gives :

	Theory.	Found.	Theory.	Found.
$\text{C}_9\text{H}_8\text{N}_2\text{O}$	67.50%	67.32%	5.00%	5.03%
	Carbon.		Hydrogen.	

By a repetition of the preparation of the methyl oxygen ether, from 30 grams of the 4-quinazolone, 14 grams of the oxygen ether were recovered by steam distillation. The residue from steam distillation was always colored a straw yellow, but no nitrogen ether was observed as present. In the above experiment, 12 grams unchanged quinazolone were recovered from the residue of the steam distillation.

Deportment of the Oxygen Ether towards Acetic Anhydride.

A small amount of the ether, about 0.1 gram, was boiled with about 3 cc. of acetic anhydride. After cooling, the anhydride was converted to acetic acid by the addition of a few cubic centimeters of water and gentle heating. The mixture on cooling in a freezing mixture, yielded long needles that filled the test-tube. On filtering, drying and melting pointing, they showed a melting point of 213°C .

Deportment of the Oxygen Ether towards HCl.

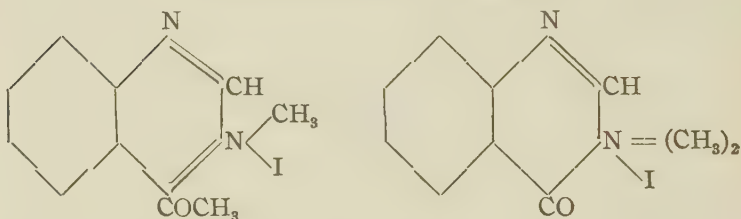
About 0.1 gram of the ether was boiled gently a few minutes in a test-tube with about 5 cc. concentrated HCl. The acid,

on cooling, was then neutralized with ammonia. On cooling in ice, the contents of the tube solidified to a complete network of crystals, needles which on filtration and drying, showed a melting point of 213°C .

4-Methoxy quinazoline had a characteristic sweet smell not unlike a faint odor of benzaldehyde. With gentle rubbing between the fingers, the compound melted easily to a thin oil.

4-Methoxyquinazoline Iodmethylete.

3-Methyl 4-quinazolone Iodmethylete.

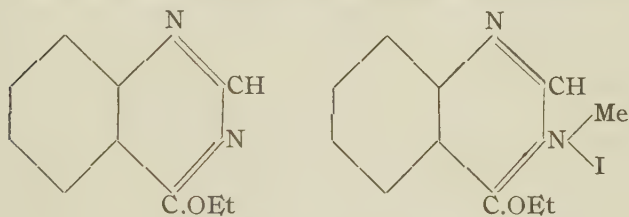


About a gram of the 4-methoxyquinazoline was heated in a sealed tube with 5 grams methyl iodide at $100-105^{\circ}\text{C}$. for 7 hours. In the cold, the reaction set in at once, yellow crystals separating before heating. After heating, the contents of the tube was a solid mass of yellowish crystals showing no signs of decomposition. The mass was dissolved directly in water in which it was readily soluble while hot. A small amount of reddish material remained insoluble. On allowing to crystallize, a good yield of short needles melting at 265°C . (corr.) were recovered. The same results were obtained by heating a gram of the ether with 6 grams methyl iodide under a water condenser, the temperature of the heating bath being maintained at $190-200^{\circ}\text{C}$., for 3 hours. The product, crystallized from water, gave short stubby needles, melting at 265°C ., showed halogen with copper oxide wire and on heating a few degrees above its melting point, showed decomposition. Yield, good.

A Carius halogen determination made on the substance melting at 265°C ., gave these results; 0.2 gram substance yielded 0.1559 gram AgI. By calculation, this gives 42.17 per cent. less iodine. The theory for iodine in $\text{C}_{10}\text{H}_{11}\text{N}_2\text{O}$, is 42.04 per cent.

In the repetition of the preparation of 3-methyl 4-quinazolone already prepared by Knape,¹⁵ it was found that when a strong excess of methyl iodide was used, the corresponding iodmethylete of the 3-methyl 4-quinazolone was formed. The iodmethylete crystallized well from the reaction mixture as colorless needles melting at 263°C ., after two crystallizations from alcohol.

4-Ethoxyquinazoline and 4-ethoxyquinazoline iodmethylete.



Six grams 4-quinazolone, 1.1 grams sodium dissolved in about 50 cc. absolute alcohol (ethyl) were heated in a sealed tube at $160-70^{\circ}\text{C}$., for 6 hours. The tube and contents were rinsed out with fresh alcohol and the alcohol evaporated. A thick oily residue remained. This was taken up in a small amount of water, owing to the presence of a small amount of sodium chloride, and distilled with steam. Oil drops came over and collected in the distillate. The watery distillate was twice extracted with ether; the extract, dried with CaCl_2 and the ether evaporated in a tared flask, yielded a residue of 1.8 grams of an oil, quite thin, slightly yellow in color and possessing an odor common to the oxygen ethers. The oil refused to solidify even in a freezing mixture.

The same ethoxyquinazoline was also prepared by the interaction of sodium ethylate and 4-chlorquinazoline at the

ordinary pressure. To this end, 10 grams 4-quinazolone were chlorinated and the total chloride formed was allowed to react with 50 cc. absolute ethyl alcohol containing 1.8 grams sodium. A very vigorous reaction set in, in the cold, with the separation of NaCl. The mixture, heated on the water bath for an hour, allowed to stand over night, then heated another hour, filtered from the NaCl and evaporated to dryness, then steam distilled and ether extracted as before, yielded 2.5 grams of oil, almost colorless and having a pleasant ethereal odor. The residue from steam distillation yielded 7 grams of a yellow warty material quite soluble in cold water and melting at 212°C . The 4-quinazolone used, melted at 214°C .

The 4-ethoxyquinazoline was made several times but only a very small amount of the oil was obtained. One time, when the operation was carried out at normal pressure, according to the latter direction, there resulted about 12 grams of a pale oil from 10 grams 4-quinazolone which was converted to chloride. In the ice box, the oil solidified to a quite firm solid. The solid crystalline lump seemed to have a small amount of oil unsolidified, so the mass was carefully pressed between filter papers and the dry product was found to melt rather sharply at $42-4^{\circ}\text{C}$. By a Dumas nitrogen, 0.2647 gram substance gave 38.6 cc. N at 25°C ., and 759 mm. Hg. Calculated, this gives 16.24 per cent. nitrogen. Nitrogen theory for $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}$ is 16.06 per cent.

One gram of the oily 4-ethoxyquinazoline was dissolved in 5 grams methyl iodide and heated in a sealed tube for an hour at 100°C . On cooling, the contents of the tube were almost a solid mass of crystals. The contents of the tube were transferred, by means of strong alcohol, to a dry beaker and evaporated carefully to get rid of the excess of methyl iodide. In changing the substance from the tube to the beaker, there was a portion of the substance difficultly soluble in the strong alcohol. However, the whole mass was dissolved and allowed to evaporate to near dryness on the water bath.

The residue was taken up in boiling water and allowed to crystallize after filtering. The yellowish red solution yielded no crystals. The red tar remaining on the filter after water extraction was taken up in alcohol, but this alcoholic solution yielded no crystals aside from a separation of a red dust-like material which was most likely a per-iodide formed as a by-product in the reaction. Owing to scarcity of material, the operation was not repeated to find out the nature of the solid which was less soluble on first treating the reaction mixture with strong alcohol.

Study of the Yellow Form of 4-Quinazolone.

Whenever an alcoholate reacted with 4-chlorquinazoline, it was found that a considerable quantity of the hydrolyzed product, 4-quinazolone, remained in the flask as a residue from the steam distillation. This same residue was always yellow colored, and the product crystallizing from the solution after concentration, was always yellow, came down in the form of warts and nodules, melting at $208-12^{\circ}\text{C.}$, and did not have the appearance of the original 4-quinazolone used. The yellow form seemed more soluble in water. It was thought that we might be dealing with the tautomeric form of the 4-quinazolone. The true 4-quinazolone as prepared in this laboratory, crystallized in fine long needles which were colorless and had a strong resemblance of paper pulp. The colorless needles had a sharp melting point and were very sparingly soluble in cold water. On the other hand, the product of hydrolysis of the chloride seemed to be quite different from the original material used in the reaction.

With the idea that one might be dealing with a tautomeric form of 4-quinazolone, which might be changed into the colorless form as we knew it, the yellow material obtained by the interaction of sodium ethylate and 4-chlorquinazoline, was heated in a sealed tube at 250°C. , for 1.5 hours. On cooling, the contents of the tube had not suffered any decomposition and the mass had crystallized in almost colorless

needles. The mass was extracted with hot water, in which it seemed less soluble than the original material. The solution was less intensely yellow than the solution from which it was obtained, in the start. On crystallizing, of 2 grams material heated, 1.5 grams were recovered in the shape of small shot-like balls; these were quite hard, and on breaking them, it seemed that their yellow coating was only on the outside of the pellets. The inside of the balls was perfectly colorless. On pulverizing the balls, the mixture took on a needle-like consistency. Melting point $210-12^{\circ}\text{C}$. The crystals, with dilute alkali, dissolved easily and were more soluble in dilute alkali, than in cold water. A gram of this same product was again heated in a sealed tube at 265°C ., for 2.5-3.0 hours, whereby the mixture suffered some decomposition. The contents of the tube were taken up in alcohol and after filtration, were evaporated to dryness. The residue, taken up in water, had only a slight yellow coloration. The residue seemed less soluble in cold water and in cold alcohol than the previously unheated material. The pale yellow solution yielded a thick network of long needles, almost colorless filaments which on drying, melted at 212°C . From 1 gram of the substance heated, 0.8 gram of the very slightly colored needles resulted. As to whether there had been an actual conversion of the yellow form of 4-quinazolone into the colorless form, simply by heating the yellow form above its melting point, or whether the yellow form, by further purification by crystallization, etc., had simply been decolorized without any tautomeric rearrangement, we are unable to say. However, there seems to be a difference in the solubilities of the colored and the colorless forms, which is hard to account for. The yellow and the white forms may be the same form of the 4-quinazolone, but there is sufficient ground to justify a further examination of the two substances.

Hand,³⁴ in his dissertation, reports that he obtained the yellow form of 4-quinazolone by allowing anthranilic nitrile

and formic acid to react. By an exhaustive treatment, he finally obtained a sample of the compound which by sublimation gave the colorless needles melting $215.5\text{--}216.5^\circ\text{C}$. Corr.

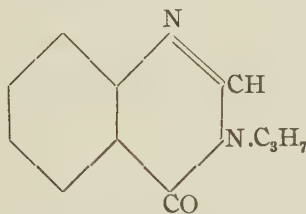
A carbon and hydrogen determination on the yellow form of the 4-quinazolone isolated by the action of sodium ethylate on 4-chlorquinazoline, gave the following figures.

0.2 gram substance gave 0.4826 gram CO_2 and 0.0760 gram H_2O .

Calculation gives a value of 65.80 per cent. carbon and 4.22 per cent. hydrogen.

The theory for $\text{C}_8\text{H}_6\text{N}_2\text{O}$ is 65.75 per cent. carbon and 4.11 per cent. hydrogen.

3-Propyl, 4-quinazolone.



To prepare this nitrogen ether, 10 grams 4-quinazolone were dissolved in 100 cc. 50 per cent. ethyl alcohol and this solution was allowed to dissolve 2.75 grams NaOH. When the mixture was heated to complete the solution of the alkali, heating being done under a water condenser and on a water bath, 12 grams normal propyl iodide were added. The mixture was then heated 4 hours, after which the reaction was neutral to litmus. On evaporating the alcoholic mixture to dryness, there remained an oily mass which solidified on cooling. This residue was then transferred to a large flask by means of water, and subjected to steam distillation. When 500 cc. of distillate were obtained, it was ether-extracted, the extract dried with CaCl_2 and freed from ether. A residue of 0.4 gram, an oil that solidified on stand-

ing, was recovered as splendid colorless needles. The mass being quite firm, was pulverized and tested by its melting point. It melted at 82°C . This product from steam distillation, on being heated in a sealed tube with strong HCl at $100\text{--}20^{\circ}\text{C}$., 1.5 hours, did not suffer hydrolysis. The original material melting at 82°C ., was obtained.

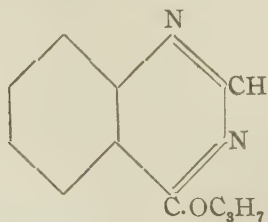
The residue from the steam distillation was then transferred to a beaker by means of alcohol, since quite a little oil had remained insoluble in the water of the distilling flask. The collected residue was brought completely into solution and the dilute alcoholic solution was allowed to evaporate until oil drops began to separate from the hot solution. The solution, on removal from the bath and allowing to crystallize, yielded fine long needles arranged in sheaves. These were filtered off and the mother liquor concentrated, when another crop of crystals resulted. From the two yields, 6.8 grams of the desired product were obtained.

On crystallization from water, in which it was fairly soluble, there were obtained fine colorless needles which melted at $82\text{--}3^{\circ}\text{C}$., sharply.

By a Dumas nitrogen determination, 0.2 gram substance melting at $82\text{--}3^{\circ}\text{C}$., gave 26.7 cc. N at 761 mm. and 24°C .

By calculation, this gives 14.98 per cent. nitrogen. The theory for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}$ is 14.89 per cent. nitrogen.

4-Propyloxyquinazoline.



8 grams 4-quinazoline were chlorinated by the method already given, and the total chloride produced, was allowed to react with 75 cc. abs. ethyl alcohol containing sodium

propylate equivalent to 1.5 grams of sodium. This propylate was prepared by treating the sodium with an excess of propyl alcohol, distilling off the excess of alcohol when the sodium was completely dissolved, and dissolving the residue in absolute ethyl alcohol. On adding this solution of the propylate to the solution of the chloride already formed, there started a reaction which was continued on a boiling water bath for three hours. The reaction mixture was freed from alcohol by heating on a water bath, in a current of air. On evaporation nearly to dryness, the residue was steam-distilled and the oxygen ether recovered from the distillate by the usual method. There was recovered a pale yellow, thin oil weighing 5.2 grams. This was taken up in ether and subjected to distillation. After the removal of the ether, the mixture immediately boiled at a constant temperature, $257-60^{\circ}\text{C}$., without any difficulty. The yield was 3.5 grams of colorless oil having a weak garlic odor. With continued boiling, decomposition set in in the residue and the distillate came over slightly yellow.

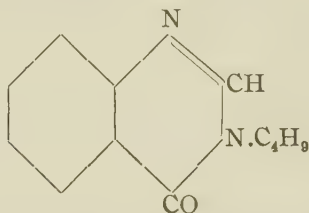
A Dumas nitrogen determination was made in the sample boiling at $257-60^{\circ}\text{C}$. with the following results: 0.1520 gram substance gave 13.6 cc. nitrogen at 22°C ., 752 mm. Hg. Calculated, this gives, 10.03 per cent. nitrogen. The theory for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}$ is 14.89 per cent. nitrogen.

The small sample of oil was again distilled and found to boil at $257-60^{\circ}\text{C}$. and another nitrogen determination was made. 0.2468 gram substance gave 17.0 cc. N at 20°C . and 767 mm. Hg. Calculated, this gives 7.95 per cent. nitrogen found.

A portion of the oil was boiled with strong HCl for about 20 minutes when the solution was made alkaline with NaOH and filtered. The excess of alkali was neutralized by means of dilute HCl. On standing a short time, there was a good yield of almost colorless crystals, nodules melting with sublimation at 212°C . sharp. On treating with NaOH solution, they dissolved readily in the cold to form a colorless

solution, which by treating with CO_2 , yielded short colorless needles melting at 212°C . sharp. This was identical with 4-quinazolone.

3-Butyl, 4-quinazolone.



10 grams 4-quinazolone were dissolved in 100 cc. of 50 per cent. ethyl alcohol; then 2.75 grams NaOH were added and the mixture heated on a water bath under a return cooler until complete solution of the NaOH had been accomplished. 12.6 Grams normal butyl iodide were added. The mixture, after heating on a water bath for six hours, was transferred to a beaker and evaporated on the water bath to near dryness; to insure the complete removal of any butyl iodide, the mixture was taken up in a small quantity of alcohol and evaporated to small volume again. The residue was transferred by means of ether to a large flask and steam-distilled. A distillate of 500 cc. was collected. On standing, a small amount of oil separated on the surface.

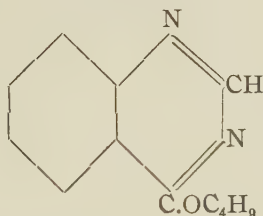
The residue in the distilling flask was transferred by means of alcohol to a beaker and evaporated to a volume of about 300 cc., when oil drops began to separate from the solution. On cooling in an ice box, the solution became full of crystals, and the oil that had separated, solidified to a quite firm cake. Yield, 7.6 grams. On evaporation of the filtrate to about 75 cc., the solution yielded 2.2 grams of the same material. By recrystallization, there resulted colorless fine needles which were very pure and showed a sharp melting-point of 73°C .

The steam distillate, by ether extraction, yielded 0.3 gram

of a semi-solid material that had a slight odor. This material was almost insoluble in water, readily soluble in ether and alcohol. Some of the material was heated in a sealed tube with a few cubic centimeters strong HCl at 110–20° C., for 1.5 hours. From the reaction mixture were obtained fine colorless needles that melted at 73° C., and were identical with the material in the major portion.

By a Dumas nitrogen determination, with some of the material non-volatile with steam and melting at 73° C., 0.2 gram substance gave 24 cc. N at 773 mm. Hg. and 22.5° C. By calculation, this gave 13.80 per cent. for the nitrogen found. The theory of nitrogen for $C_{12}H_{14}N_2O$ is 13.86 per cent.

4-Butyloxyquinazoline.

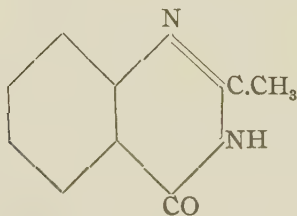


8 Grams 4-quinazolone were converted to chloride in the usual way and were heated with 75 cc. absolute ethyl alcohol containing sodium butylate equivalent to 1.3 grams sodium. The butylate was prepared in an analogous way to the preparation of the preceding propylate. Absolute normal butyl alcohol was used. When the ethyl alcoholic solution of sodium butylate was mixed with the chloride already prepared, a vigorous reaction set in. The mixture was then heated on a water bath three hours under a return cooler. The neutral solution was transferred by means of alcohol to a large flask which was heated on a water bath. With a current of air, the alcohol was removed and the reddish yellow residue of salt and the resulting oxygen ether were then subjected to steam distillation. The main portion of the distil-

late, by ether extraction, yielded 2.8 grams of a light-yellow thin oil possessing an ethereal odor. By means of dry ether, the oil was placed in a distilling flask and subjected to distillation. The main portion of the distillate boiled at $263-5^{\circ}\text{C}$., normal pressure. A few drops of the distilled oil were dissolved in about 8 cc. strong HCl, in which it dissolved readily, and boiled gently for a few minutes. The excess of HCl was removed, the yellow acid solution was then neutralized with NaOH in excess and filtered. A very small amount of oily material remained on the filter. On neutralizing the colorless alkaline solution with dilute HCl to permanent turbidity and placing the turbid solution in the ice box, a flocculent separation of colorless crystals occurred. The crystals were easily soluble in alkali and melted at $211-12^{\circ}\text{C}$.

Two Dumas nitrogen determinations were made on the oil distilling at $263-5^{\circ}\text{C}$.; 0.2542 gram of the substance gave 15.8 cc. nitrogen at 22°C ., 752 mm. Hg. Calculation gives a nitrogen value of 6.96 per cent. 0.1962 gram substance gave 12.4 cc. nitrogen at 23°C ., and 758 mm. Hg. By calculation, this gives 7.10 per cent. nitrogen. The theoretical nitrogen value for 4-butyloxyquinazoline is 13.90 per cent.

2-Methyl, 4-quinazolone.



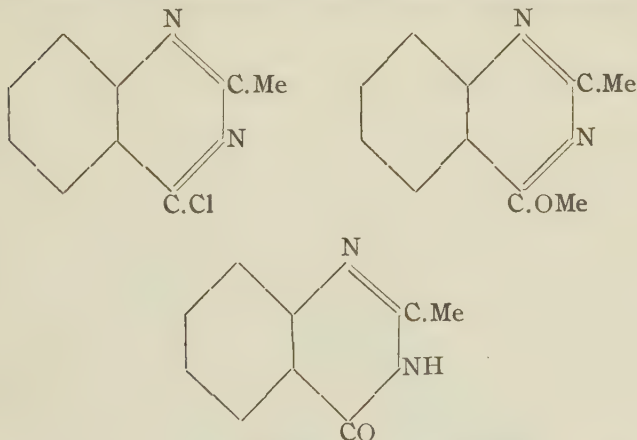
This compound has already been reported in the literature³⁰ and was made in this laboratory by treating anthranilic acid with an excess of acetic anhydride, removing the excess of anhydride by low evaporation, and converting the resulting acetanthranil into 2-methyl, 4-quinazolone by means of

aqueous ammonia. The quinazolone, separated from the alkaline mixture as an amorphous mass, was dissolved in dilute alkali and thrown out of solution in a quite pure state by means of CO_2 . Melting point 235°C .

Chlorination of 2-Methyl, 4-Quinazolone.

The work of Dehoff¹⁴ was repeated in order to either obtain his tetrachlorquinazoline, or to obtain the simple 2-methyl, 4-chlorquinazoline, which is possible theoretically. The directions of Dehoff were followed in detail, except that double the quantity of PCl_3 was found to give better results than he reported. By using double the quantity of PCl_3 recommended, a less colored end-product resulted. Where Dehoff obtained a brown sandy powder, by using more PCl_3 , an almost colorless product resulted. After treatment with dilute NaOH , the insoluble amorphous mass was crystallized from dilute alcohol. Melting point $124-25^\circ \text{C}$. No decolorization with charcoal was necessary.

4-Methyl oxygen ether of Dehoff's tetrachlorquinazoline.



3.2 grams of the chloride just mentioned, crystallized from dilute alcohol, were allowed to react with about 35 cc.

absolute methyl alcohol containing 0.32 gram sodium. The reaction was carried on in a sealed tube at $110^{\circ}\text{C}.$, for 3.5 hours. The contents of the tube were washed into a distilling flask by means of methyl alcohol and the alcohol was then removed by distillation on a water bath. When the alcohol was removed, the residue was distilled with steam. The desired oxygen ether distilled over quite slowly, but there was a constant turbid distillate delivered. Particles of the ether solidified in the tube of the condenser and in the distillate. By ether extraction, etc., as usual with the steam distillate, there was obtained a slightly yellow oil as a residue. This crystallized immediately on cooling, in the shape of radiating bundles of crystals which became quite hard on gentle agitation and standing for a short time. The compound had a peculiar ethereal odor much like the corresponding 4-methoxyquinazoline melting at $35.4^{\circ}\text{C}.$

The methyl oxygen ether of Dehoff's tetrachlorquinazoline gave a good Beilstein test for halogen, and gave hard crystals melting at $87-8^{\circ}\text{C}.$ Yield, 2.4 grams pure ether.

By a Carius halogen determination, 0.2 gram material gave 0.3098 gram AgCl , which by calculation gives 38.24 per cent. Cl .

The theory for $\text{C}_{10}\text{H}_7\text{N}_2\text{OCl}_3$ is 38.37 per cent. chlorine.

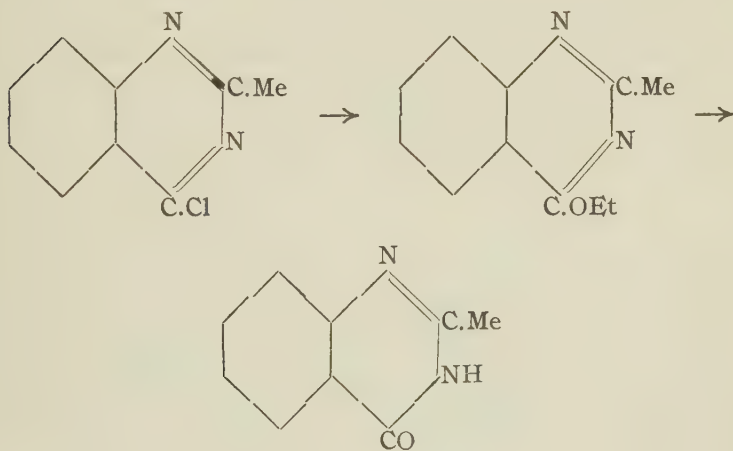
Depoiment of the Methyl Oxygen Ether towards Strong HCl.

About 0.1 gram of the ether melting at $87-8^{\circ}\text{C}.$, was heated under a reflux condenser, on a gauze, with about 10 cc. concentrated HCl . Gentle heating was continued for about 15 minutes. The mass went completely into solution, when suddenly the solution became a mass of short heavy colorless needles. On dilution with water and heating to boiling, the solution was allowed to cool. The crystals, remaining almost insoluble in hot water, were filtered, dried and a melting point taken. They melted at $206-7^{\circ}\text{C}.$, and were identical with the Bz. trichlor, 2-methyl, 4-quinazolone prepared by Dehoff.¹⁴

Action of Alcoholic NaOH on the Tetrachlor, 2-Methyl Quinazoline.

1.5 grams of the crystallized chloride, 0.2 gram NaOH and 30 cc. absolute ethyl alcohol were mixed in a flask and evaporated on a water bath to dryness. The evaporation was done in a flask to insure slower evaporation. A slightly reddish mass was left behind. This was repeatedly extracted with hot water, in which it seemed very insoluble. The oily mass, on cooling, solidified to a slightly colored hard globule in the pit of the filter. The lump was dissolved in strong alcohol, water was added to a permanent turbidity, heated until the turbidity had disappeared, then allowed to cool. The solution yielded 0.75 gram colorless, flaky glistening leaflets melting at $72-3^{\circ}\text{C}$. Instead of replacing the 4-Cl atom with a hydroxyl, the alcoholic NaOH had reacted to form the ethyl oxygen ether of the tetrachlor-quinazoline.¹⁴

By boiling with strong HCl, a short time under a condenser, the ether was hydrolyzed and Bz. trichlor, 2-methyl, 4-quinazolone separated as short needles from the acid solution. Melting point $206-7^{\circ}\text{C}$.

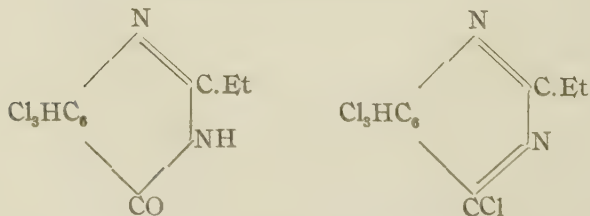


In each of the above quinazoline rings, there are three chlorine atoms; they are located on the benzene nucleus, but their exact position is unknown.

Hydrolysis of Tetrachlorquinazoline by means of Aqueous NaOH.

The hydrolysis of Dehoff's tetrachlorquinazoline by means of NaOH is a very unsatisfactory operation. 2 grams of the chloride, freed from any 2-methyl, 4-quinazolone by washing with hot dilute NaOH previous to starting the hydrolysis, were suspended in about 100 cc. 10 per cent. NaOH solution and boiled four hours under a return condenser. At the end of this time, the solid had gone almost completely into solution, thus indicating that the chloride had been converted into the 2-methyl, Bz. trichlor, 4-quinazolone which was easily soluble in hot dilute NaOH. On allowing the solution to cool and acidifying with HCl, no appreciable separation was observed. On making the solution alkaline with NaOH and passing CO₂ through the solution a long time, only a slight separation was observed. The solution was filtered and the filtrate evaporated to dryness, taken up in hot strong alcohol and allowed to crystallize. By the evaporation of the alcoholic solution, there remained a small amount of light fluffy, soft, yellow crystals not melting below 250° C. The main portion of the products of hydrolysis had remained soluble after treating with HCl and CO₂.

2-Ethyl 4-quinazolone.



In a manner analogous to the preparation of 2-methyl

4-quinazolone from acetantranil and ammonia, we hoped to be able to prepare 2-ethyl 4-quinazolone in as good a yield from propionyl anthranil and ammonia. To prepare the anthranil, 10 grams anthranilic acid and 10 grams propionic anhydride were heated in a beaker at such a rate that in the course of 15 minutes, the excess of anhydride and propionic acid had been boiled out. The oily mass became glasslike, hard but still not crystalline. The mixture was now heated with 20 grams acetic anhydride which was removed by boiling over a small flame. About one-half hour's heating was required to remove the acetic anhydride and acetic acid. The residue from the dehydration process was a solid yellowish crystalline mass showing no signs of decomposition. The mass was taken up in 50 cc. strong ammonia; the solid mass refused to go into solution, but melted to a thin oil. On cooling the solution after it had been boiled about 15 minutes, quite a little solid material separated from the solution. The crystals were filtered and after washing with water, were dissolved in hot dilute NaOH solution. The yellowish solution was then cooled and treated with CO_2 . An almost colorless amorphous product separated. 5 grams material melted at 214°C . On crystallization from CCl_4 in which it was quite soluble on heating, and quite insoluble on cooling, it yielded a very pure product with a less sharp melting point than the formed substance. From CCl_4 , melted $210-16^\circ\text{C}$. Flakes. The original substance, recrystallized from boiling alcohol, gave a small amount of feathery needles melting $230-31^\circ\text{C}$. The 2-ethyl 4-quinazolone melted 234°C ., according to the literature.

The compound melting at 214°C ., soluble in dilute alkali and precipitated by the action of CO_2 , gave the following results by analysis. By a Dumas nitrogen determination, 0.2 gram material gave 24.6 cc. N at 23°C ., and 765 mm. Hg. Calculated, this gives 13.95 per cent. nitrogen. 0.2 gram material also gave 28.6 cc. N at 26°C . and 764 mm. Hg. By calculation, this gives 14.84 per cent. nitrogen. By a

carbon and hydrogen determination, 0.2 gram material gave 0.5045 gram CO_2 and 0.0960 gram H_2O . By calculation, this gave a value of 8.33 per cent. hydrogen and 68.79 per cent. carbon. The unknown compound was not studied further.

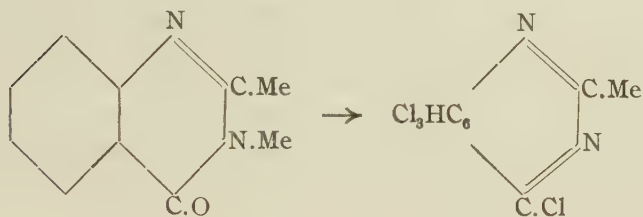
The filtrate obtained in the previous experiment from the filtration of the solid separating after the reaction of propionyl anthranil and ammonia, was again heated to boiling for some time. On cooling, the solution was filtered, the residue washed and dissolved in dilute NaOH . On passing CO_2 into the solution, there was a separation of quite a little solid. The colorless amorphous crystals were filtered and found to melt at 230°C ., 2 grams recovered.

Chlorination of 2-Ethyl 4-Quinazolone.

1.7 grams of the 2-ethyl 4-quinazolone prepared above, were heated in a sealed tube with 3 grams PCl_5 and 15 cc. PCl_3 , at 165°C . for 3.5 hours. The contents of the tube, which were only slightly pink, were transferred to a distilling flask by means of fresh PCl_3 and the excess of POCl_3 and PCl_3 were removed by distillation. The residue was then treated with cold water and dilute alkali; when alkalinity was established, the solution changed from a red to a pale yellow color. The strongly alkaline solution was then heated to boiling to dissolve out any unchlorinated 2-ethyl 4-quinazolone. On cooling, the solution was filtered. The residue, dissolved in strong alcohol, was then boneblackened, filtered and evaporated to about 50 cc. in volume. With the addition of an equal volume of water, the solution at once became turbid with the separation of crystals which were small, slightly yellow needles melting at $85-7^\circ\text{C}$. This alcohol-water treatment was repeated twice more and a very pure product resulted. Melting point from dilute alcohol, 80°C . By a Carius halogen determination, 0.2 gram substance gave 0.3885 gram AgCl . Calculated, this gives

47.94 per cent. Cl found. Theory for chlorine in $C_{10}H_6N_2Cl_4$ is 47.97 per cent.

2,3-Dimethyl 4-quinazolone.



2,3-Dimethyl 4-quinazolone was prepared by two methods, by the action of methylamine and acetantranil, and also by the methylation of 2-methyl 4-quinazolone by means of alkali and alkyl halide.

By the first method, anthranilic acid was converted to acetantranil which was crystallized from acetic acid. 10 grams of the anthranil, mixed with 10 grams 30 per cent. methylamine solution diluted to about 150 cc., were heated under a return condenser $\frac{1}{2}$ – $\frac{3}{4}$ hours. Then a few drops of strong KOH solution were added and the excess of amine distilled. The cooled contents of the flask yielded a heavy crop of crystals that were crystallized from water. Yield, 9 grams 2,3-dimethyl 4-quinazolone.

By the second method, 10 grams 2-methyl 4-quinazolone were dissolved in 100 cc. of about 75 per cent. methyl alcohol; 3 grams NaOH were added and the mixture was warmed gently until solution of the NaOH was complete. Then 12 grams methyl iodide, in small portions at a time, were added, meanwhile heating the reaction mixture on a water bath, under a return cooler. After heating 4–5 hours, the mixture was transferred to a beaker and evaporated to dryness. The residue was extracted with ether, which yielded on evaporation 8 grams yellowish nodules having a slight ethereal odor. The residue was steam-distilled and yielded a slightly turbid distillate containing a small quantity of

crystals on the surface. By evaporation of the distillate in the air, a residue was left. Melting point $105+^{\circ}\text{C}$. Although all due precaution had been taken in the distillation, it was found that some of the nitrogen ether had gone over with steam. About 0.1 gram of the substance melting $105-6^{\circ}\text{C}$., had appeared in the steam distillate. Strong HCl failed to change the melting point by boiling the residue with strong HCl a short time. The residue in the original distilling flask, by evaporation to dryness two or three times with strong alcohol, yielded 7 grams 2,3-dimethyl 4-quinazolone.

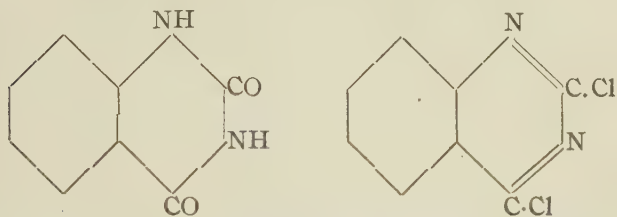
Chlorination of 2,3-Dimethyl 4-Quinazolone.

Fisher,²⁴ working with N-alkyl pyridones, succeeded in replacing the oxygen atom of the carbonyl group with two atoms of chlorine with the subsequent elimination of alkyl chloride, leaving the nitrogen atom unsubstituted and only one halogen atom in the molecule. Working with the notion that we might be able to chlorinate this quinazolone in an analogous manner, the same treatment was given 2,3-dimethyl 4-quinazolone.

5.7 grams 2,3-dimethyl 4-quinazolone were heated with 5 grams PCl_5 and 25 cc. POCl_3 in an air bath at the boiling point of the mixture. The solution became quite red, and after five hours' heating almost all the solid matter had gone into solution. The reaction mixture was washed with fresh POCl_3 into a distilling flask and the excess of phosphorus halides removed by distillation. Vacuum distillation and water bath heating at the last of the distillation, were used. The red residue remaining in the flask was allowed to react with 1.0 gram sodium dissolved in 75 cc. absolute methyl alcohol. A vigorous reaction set in, and then the mixture was heated on a water bath, for two hours under a water condenser. The mixture was treated with 0.5 gram sodium and heated another hour. On removal of the alcohol, and steam distillation, a turbid distillate with oil drops solidifying partly on standing, was obtained. With ether extraction,

a gram of oil resulted. This oil solidified on standing and showed halogen by means of a copper oxide wire. By boiling gently with a few cubic centimeters strong HCl, and evaporation, followed by re-solution in water, long colorless needles separated. Melting point, $203-5^{\circ}\text{C}$. This was identical with 2-methyl, Bz. trichlor 4-quinazoline.

Benzoylene urea and 2,4-dichlorquinazoline.

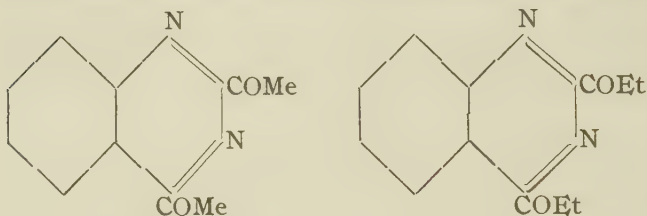


Benzoylene urea was prepared by the direct fusion of molecular quantities of anthranilic acid and urea. In this fusion, considerable decomposition takes place and the yield of crude diketo-quinazoline is small. From 100 grams anthranilic acid, only 39 grams benzoylene urea were obtained. After fusion, the mass was extracted with hot water and the insoluble residue was filtered, dissolved in dilute hot NaOH and thrown out again by means of CO_2 . A very pure product resulted.

The chloride was made according to Abt,¹² by means of heating benzoylene urea in a sealed tube with two moles PCl_5 and some PCl_3 . The chlorinated product was freed of phosphorus halides by distillation under diminished pressure. By continued heating, the chloride showed tendencies towards sublimation, but the residue suffered such decomposition that it was thought useless to try any purification by this method, that is, for large quantities. It was found that the chloride was reasonably pure after the removal of the halides of phosphorus providing the heating was not carried on any longer than was absolutely necessary. With continued heating, the mass darkened and finally charred; so in the

experiments where the chloride was used, the residue was completely melted with a small flame and poured out of the distilling flask. The oil immediately became solid and was used in this shape for subsequent work.

2,4-Dimethoxyquinazoline and 2,4-diethoxyquinazoline.



2,4-Dimethoxyquinazoline had been made by Abt,¹² but it was also prepared in this laboratory to see how the 2,4-dichlorquinazoline prepared here, would work to give a known compound. By heating 2 grams of the chloride with 0.5 gram sodium in 50 cc. absolute methyl alcohol at 100° C., under a reflux condenser for three hours, 0.5 gram of the desired 2,4-dimethoxyquinazoline melting at 67° C., was recovered after the second crystallization from dilute alcohol. In this experiment, the compound separated directly from the reaction mixture without any further treatment. In subsequent work, it was found a very good scheme when the reaction was complete, to evaporate the mixture, previously filtered free from NaCl, down to dryness and then subject the residue to steam distillation. By this means, the unchanged quinazoline and dimethoxyquinazoline were separated. The steam distillate, turbid at first, soon yielded the ether as a solid mass. The distillate could be filtered or treated with a small amount of alcohol until all the solid had dissolved, heated and cooled again, whereupon the ether usually came down in fine long needles. The ether is very easily soluble in hot alcohol, while in boiling water, the ether dissolves only very slightly.

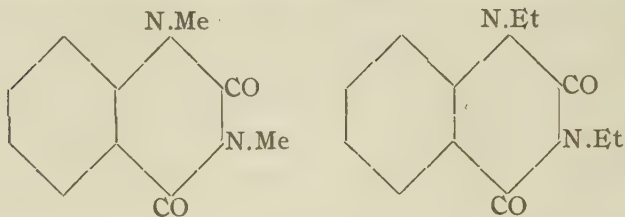
In the preparation of 2,4-diethoxyquinazoline, 6 grams benzoylene urea were chlorinated, freed from phosphorus halides by reduced pressure distillation, and heated with about 50 cc. absolute ethyl alcohol containing 2 grams sodium. The heating was on a water bath, conducted under a return water condenser for 3.5 hours. The NaCl was removed by filtration and the filtrate evaporated to near dryness. The residue, taken up in a small amount of water, was then subjected to steam distillation, with which was obtained a distillate containing oil drops. By allowing to stand in the ice box, the distillate yielded 2 grams of a very pure solid melting at $50-1^{\circ}\text{C}$.

A Dumas nitrogen determination gave the following figures: 0.15 gram material gave 17.1 cc. N at 22°C . and 757.5 mm. of Hg. Calculated, this gave 12.81 per cent. nitrogen. Theory for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}$ is 12.84 per cent. nitrogen.

About 0.1 gram of the 2,4-diethyl benzoylene urea was heated under an air condenser, in a small flask with a few cubic centimeters strong HCl. After gentle boiling for about five minutes, the solution was made alkaline with NH_4OH . A crystalline deposit resulted. The bulk of the deposit was slightly less than that of the starting material. The crystals were filtered, washed with water, in which it was insoluble and tested by its melting point. The crystals were soluble in dilute NaOH, precipitated by HCl or CO_2 . Melting point, $325-30^{\circ}\text{C}$.

0.4 gram of the oxygen ether were heated with 4 grams methyl iodide in a sealed tube for two hours at $110-15^{\circ}\text{C}$. The highly colored contents of the tube were washed into a beaker with 95 per cent. alcohol and evaporated to dryness. The solid mass was taken up in water, filtered hot and allowed to crystallize. Slightly colored flaky crystals separated; on crystallization from water, the crystals showed a melting point of $262-3^{\circ}\text{C}$., uncorr. With copper oxide wire, the crystals showed the presence of halogen.

1,3-Dimethyl benzoylene urea and 1,3-diethyl benzoylene urea.



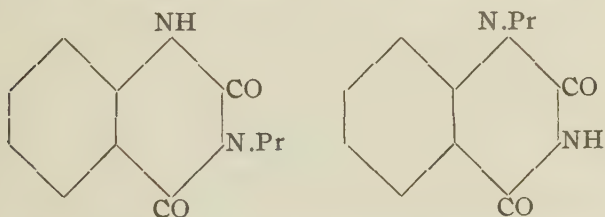
2 grams benzoylene urea, 1 gram NaOH and 6 grams methyl iodide were heated together in 50 cc. of about 50 per cent. methyl alcohol. The heating was carried out under a water condenser, on a water bath for four hours. The alcoholic solution was then evaporated to about one-third its volume and allowed to stand over night. Beautiful rosettes of needles separated. 1.9 grams of crystals melting at $95-147^{\circ}\text{C}$. were recovered. By recrystallization from dilute alcohol the crystals melted at $147-52^{\circ}\text{C}$. Thinking there might be a trace of impurity such as the presence of oxygen ether, the whole mass melting at $147-52^{\circ}\text{C}$. was then paced in a small flask under a cooler, and heated to gentle boiling for a few minutes with 5-10 cc. concentrated HCl. The solution was neutralized with NaOH and filtered while hot; the filtrate yielded fine colorless needles melting $163-5^{\circ}\text{C}$. Halogen-free, by copper oxide wire. By a Dumas nitrogen determination, 0.1 gram substance gave 13.2 cc. N at 22.5°C ., and 763.5 mm. Hg. Nitrogen found was 14.99 per cent. Nitrogen theory for $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}_2$ is 14.74 per cent.

This same dimethyl nitrogen ether was made by Abt in the same manner. For the melting point he assigned 151°C ., and also stated that the melting point was not changed by boiling the compound with strong HCl in a sealed tube.

1,3-Diethyl benzoylene urea was prepared by allowing ethyl iodide to react with the sodium salt of benzoylene urea, in an alcoholic solution. Two grams benzoylene urea were dissolved in about 100 cc. of approximately 50 per cent. ethyl alcohol to which a gram of NaOH was added. When

complete solution was attained, the mixture was cooled and 4 grams ethyl iodide were added. The mixture was heated under a reflux condenser, on a water bath at a temperature that just barely boiled the mixture. The heating was continued for three hours, when the solution was evaporated to one-fourth its volume, allowed to stand on cooling, and finally filtered from the product that had separated as an oil and solidified. By ether extraction of the filtrate, the major portion of the nitrogen ether was recovered. By crystallization from alcohol, a product melting at $100-50^{\circ}\text{C}.$, was recovered. By boiling this product a short time with strong HCl , the melting point of the colorless needles separating from the neutralized solution was the same as before the acid treatment. A portion of the crystals was washed with dilute NaOH solution, in which the crystals were quite insoluble even on heating; on cooling the solution, colorless needles remained. The alkali treatment removed any benzoylene urea that might have contaminated the crystals for they melted sharply at $105-6^{\circ}\text{C}.$ By a Dumas nitrogen, 0.1075 gram substance gave 12.35 cc. N at $22^{\circ}\text{C}.$, and 758 mm. Hg . By calculation, this gives 12.98 per cent. nitrogen. The theory for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_2$ is 12.84 per cent. nitrogen.

1-Propyl benzoylene urea or 3-propyl benzoylene urea.



4 grams benzoylene urea were dissolved in 100 cc. 50 per cent. ethyl alcohol containing 2 grams NaOH . The mixture was heated on a water bath, under a return cooler, until complete solution; then 9.5 grams normal propyl iodide, in small portions at a time, were added. The heating

was continued on the water bath for eight hours. On removal of the alcohol, the residue was steam-distilled. The water solution in the distilling flask was cooled and found to yield a solid crystalline mass. In boiling solutions, the mass melted to a sticky oil. The solid mass, 3.7 grams, was extracted repeatedly with hot water in which it was sparingly soluble. The extracts yielded fine small hard colorless crystals melting at 171°C . The residue from the hot water extractions was finally allowed to dissolve in hot alcohol. Enough water was added to the solution to give a permanent turbidity on cooling. On standing a long time, about 0.5 gram of crystals melting at $175-6^{\circ}\text{C}$., resulted. This was most likely a mixture of benzoylene urea and the monopropyl derivative. The last filtrate was then given an excess of water. On standing in the ice box, at first an oil separated, but finally the solution deposited crystals which were filtered out, dissolved in dilute NaOH and precipitated with CO_2 . There was a very clean separation of fine colorless needles melting at 171°C . The same deportment towards NaOH solution was shown by the material first isolated and found to melt at 171°C . By a nitrogen determination by Dumas, 0.2 gram substance melting at 171°C . gave 24.3 cc. nitrogen at 21°C ., and 758 mm. Hg. Nitrogen found, 13.79 per cent. Calculated for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_2$, the theory is 13.73 per cent. nitrogen.

Dipropyl Benzoylene Urea.

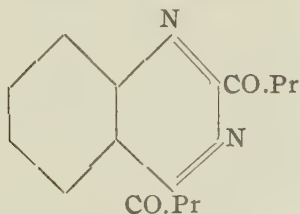
2 grams benzoylene urea were dissolved in 50 cc. of 50 per cent. ethyl alcohol containing 0.8 gram NaOH. When solution was complete on gentle heating, 7 grams normal propyl iodide were added and the reaction mixture was heated on a water bath, under a return cooler. After an hour's heating, 2 grams more of the iodide were added and heating continued for three hours. The flask containing the reaction mixture was then disconnected from the condenser and warmed gently to remove the excess of alcohol and iodide, then filtered and allowed to stand. The green colored

alcoholic solution became almost a solid mass of soft flaky colorless crystals which were filtered and found to melt at 171°C . These crystals were dissolved in dilute NaOH and precipitated by the passage of CO_2 into the solution until it was nearly neutral. There were obtained 1.8 grams of material melting at 171°C ., and identical with the mono-propyl benzoylene urea already isolated. No other product of the reaction was observed.

The preparation of 1,3-dipropyl benzoylene urea from the mono-propyl derivatives was tried. 0.2 gram sodium was dissolved in about 30 cc. (N) propyl alcohol and to this solution was added a gram of the mono-propyl benzoylene urea purified by means of NaOH and CO_2 . The mixture was heated under a reflux air condenser with 3 grams (N) propyl iodide; after heating for four hours at the boiling point of the mixture, the solution was filtered and freed from alcohol; the resulting residue was steam-distilled but nothing was recovered from the steam-distillate. In the distilling flask, there remained an oily residue which was dissolved in warm dilute alkali and treated with CO_2 . Colorless needles, 0.83 gram melting at 171°C ., separated from the solution. This was identical with the mono-propyl benzoylene urea found above.

Abt,¹² by the action of methyl iodide on the sodium salt of 3-methyl benzoylene urea, was able to form the 1,3-dimethyl benzoylene urea already prepared in this laboratory by the action of methyl iodide on the di-sodium salt of benzoylene urea.

2,4-Dipropyloxyquinazoline



5 grams benzoylene urea were chlorinated according to the directions of Gabriel,³¹ by heating under a condenser with 12 grams PCl_5 and 25 cc. POCl_3 . Solution of the benzoylene urea occurred in about half an hour; the reaction mixture was heated another hour and the dark red solution subjected to distillation under reduced pressure to free the chloride from phosphorus halides, meanwhile heating the distilling flask in a boiling water bath. The residue from distillation, containing the amount of chloride corresponding to the benzoylene urea started with, was treated with about 73 cc. absolute ethyl alcohol containing sodium propylate corresponding to 1.5 grams sodium. The propylate was prepared as in the former case with 4-propyloxyquinazoline. The reaction mixture was then heated four hours under a water condenser at the boiling point of the mixture. The neutral solution was then poured into a large flask and the alcohol evaporated in a current of air. By steam distillation and ether extraction of the distillate, which had separated into oil drops that had more or less solidified, there remained 4.1 grams of an oily product that refused to solidify. The material was again distilled with steam, whereby a very pure product resulted. Colorless oil drops separated in the solution and on standing in the ice box, the oil solidified and the solution yielded also fine long needles. The globules were dipped out on to filter paper and dried, when they seemed to be a soft oily substance. By continued steam distillation, 0.8 gram of the same waxy material was obtained. The contents of the distilling flask contained a small film of highly colored oil non-distillable with steam, and also some benzoylene urea which had resulted from the partial hydrolysis of the di-propyloxyquinazoline. The turbid solution from the last steam distillation, yielded fine long fragile needles, in small quantity. On collecting and drying, they were found to melt at $40-1^\circ\text{C}$. A portion of the waxy material was boiled gently with about 10 cc. strong HCl . On heating about five minutes over a moving burner, crystals suddenly appeared in the solution of boiling acid. They were short thick needles,

colorless and insoluble in strong acid. The excess of acid was then neutralized with NaOH and the quantity of crystals increased. From the neutral cold solution, there was obtained a very clean separation of benzoylene urea. The HCl treatment had completely hydrolyzed the dipropyl oxygen ether. The crystals melted at $350-55^{\circ}\text{C.}$, and were easily soluble in dilute warm alkali. By Dumas nitrogen determination, 0.2 gram of the substance melting at $40-1^{\circ}\text{C.}$, gave 23.2 cc. N at 25°C. , and 752 mm. Hg. Calculated, this gives 12.79 per cent. nitrogen. The theory for nitrogen in $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_2$ is 11.38 per cent. On recrystallization from water, in which the compound was sparingly soluble, crystals melting at 40°C. , were obtained. A Dumas nitrogen gave the following figures; 0.2 gram substance gave 20.2 cc. N at 23°C. and 767 mm. Hg. Calculated, this gave 11.50 per cent. nitrogen.

Alkylation of 2-Quinazolone.

The general method already given for the preparation of oxygen ethers was tried with 2-quinazolone. The latter, melting at $223-5^{\circ}\text{C.}$, was prepared in good yield by fusion of *o*-aminobenzaldehyde and urea,²⁴ and was converted into 2-chloroquinazoline, melting at $107-8^{\circ}\text{C.}$, by means of POCl_3 .²³

2-Methoxyquinazoline.

By heating 1.0 gram pure chloride in 25 cc. absolute methyl alcohol containing 0.25 gram sodium, under a condenser for three hours, on a boiling water bath, then evaporating the alcohol and subjecting the residue to steam distillation, from the distillate about 0.8 gram of an oil was recovered. On cooling, the oil became a solid mass of beautiful needles melting sharply at $55-6^{\circ}\text{C.}$ No analytical figures were obtained on the low-melting product from steam distillation. By heating in a sealed tube with concentrated HCl at $100-20^{\circ}\text{C.}$, for 1.5 hours, the oxygen ether was hydrolyzed. The acid solution, after heating, was evaporated low and

taken up in dilute alkali, neutralized with dilute HCl and allowed to crystallize in the ice box. The original quinazalone, melting at $223-4^{\circ}\text{C}$., separated as a greenish amorphous powder; easily soluble in alkali and precipitated by CO_2 .

2-Ethoxyquinazoline.

3 grams 2-chlorquinazoline were heated under a return cooler, on a water bath for four hours, with 50 cc. absolute ethyl alcohol containing 0.75 gram sodium. The reaction mixture was evaporated free of alcohol and distilled with steam. From the distillate was recovered 1 gram of a yellow oil that solidified in the ice box to an oily mass of cubical crystals. They were quite oily and so no melting point was taken. The whole mass was boiled with strong HCl, and then neutralized with dilute alkali. The neutral solution yielded greenish amorphous particles that melted at $223-4^{\circ}\text{C}$. The oxygen ether had been hydrolyzed to the 2-quinazalone.

Appendix.

In order to form a quinazolyl oxygen ether of a quinazoline, two quinazoline residues united by means of an oxygen atom, equimolecular quantities of 4-chlorquinazoline and the potassium salt of 4-quinazalone were allowed to react. The latter was made by the evaporation to dryness of an aqueous solution of 4-quinazalone and the calculated amount of NaOH. The powdered potassium salt was suspended in a benzol solution of 4-chlorquinazoline and boiled for several hours. At the end of that time, no evidence of ether formation was shown. In the same manner, 4-chlorquinazoline was allowed to react with the potassium salt of 2-methyl 4-quinazalone in a benzol solution. No ether formation was observed.

Summary.

With the alkali salts of 4-quinazolone and benzoylene urea, alkyl halides yield only the respective alkyl nitrogen ethers.

With 4-chlorquinazoline and 2,4-dichlorquinazoline, by the action of sodium alcoholates, only the respective oxygen ethers result.

The quinazoline oxygen ethers studied are quite stable and do not readily rearrange to the tautomeric nitrogen ether.

The physical and chemical properties of the oxygen and nitrogen ethers, as far as studied, conform to those reported in the literature by Meyer,³² and others.

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BIOGRAPHY.

Clarence Earl May, at the age of 15, entered Indiana University (1900) and continued the prescribed course of study in chemistry leading to the degree of B.A., which was granted in 1904. The following year was devoted to graduate work in organic chemistry leading to the degree of M.A., which was granted in 1905. During the years 1904-6, he held a single assistantship, a double assistantship and an instructorship in the Indiana University Chemistry Laboratories. He entered Columbia University and continued his graduate work during the years 1906-7 and 1907-8, carrying on this line of research under Prof. M. T. Bogert in the Department of Organic Chemistry. During the year 1907-8, he held one of the University Fellowships granted by the University.

